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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/660,924
Filing Date: September 12, 2003
Appellant(s): LATTA, PAUL P.

Daniel E.Altman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/04/05 appealing from the Office action mailed 05/18/05

(1) Related Appeals and Interferences

A statement identifying the real party of interest is containing in the Brief

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(I) Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide **enablement** for a method of preventing onset of Type I diabetes in any mammal , including human comprising implanting insulin-producing cells encapsulated in a biologically compatible membrane.

The specification only discloses the effects of the implanting of insulin-producing cells on the level of blood glucose using streptozotocin-induced diabeties in murine experimental model, using NOD mouse. (See Examples 1-2 in particular). Examples 3-7 in the instant Specification are prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed. The specification does not adequately teach how to effectively prevent onset of type I diabetes in any mammal predisposed to type I diabetes , comprising implanting insulin-producing cells encapsulated in a biologically-compatible membrane. Atkinson et al. .,(Nature, 1999, V.5, pages 601-604) teach that in addition to certain NOD strain-specific characteristics that distinguish these mice from humans at risk for type I diabetes important genus-specific features distinguish the murine diabetes as well, such as resistance to ketoacidosis or the absence of the murine homolog of HLA-DR molecules on APC. Investigators have not always considered that. **Unfortunately, in a genetically heterogeneous human population containing individuals at high risk of type I diabetes development, there is little evidence that many of them would have a comparable set of immune deficiencies that prove as malleable** (emphasis

added). In NOD mice, type 1 diabetes development is well-choreographed. In contrast, the natural history of type 1 diabetes in human is such that the age of disease onset is extremely broad; symptoms occur at any time from the first years of life to well beyond 50 years of age. It is clear that the genus-unique and strain-specific aspects of diabetes in NOD mice must be fully understand and appreciated if we are to know which therapeutic protocols are reasonable to extrapolate to humans and which are not. Exploitation of the NOD genome for clinical research is yet to be done (see pages 602, 603 and 604 in particular). Knip M (Acta Pediatr. Suppl., 1998, V.452, pages 54-62) teaches that currently the state of the art is that successful prevention of type I diabetes has at least two precondition. First, one must be able to identify individuals at increase risk for progression to type I diabetes and second, must have an intervention modality with less severe adverse effects than those associated with disease itself. Total eradication of clinical type I diabetes cannot be expected in the next century, as it is probable that a combination of different interventions will be needed to achieve an optimal effect (see entire document, page 60 in particular). Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. **The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans** (emphasis added) . Teuveson et

al., (Immun. Review 1993, N136, pages 101-107) teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in human (see page 100 in particular). Teuveson et al., further teach that " however today's small animal models seem to be insufficient to produce data for clinical decision-making" and further raises doubt as to whether large animal models can be applied to clinical situations, due to species-specific reactions to treatment (see page 101 in particular). Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". , Cochlovius et al (Modern Drug Discovery, 2003, pages 33-38) teach that in contrast to in vitro models, and partly animal-human xenograft systems, tissue cells in vivo seems to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously in vitro but a fairly high portion of them still fail *in vivo*.

Substantiating evidence may be in the form of animal tests, which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746. However, as has been discussed

supra, the state of the art is that it is unpredictable form the *in vivo* murine data using NOD model disclosed in the specification as whether the instant invention can be used for the *in vivo* preventing onset of type I diabetes in mammals including human.

Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of preventing onset of type I diabetes in mammal predisposed to type I diabetes , comprising implanting insulin-producing cells encapsulated in a biologically-compatible membrane. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of the claimed method of preventing onset of Type I diabetes in any mammal, including human are fraught with uncertainties.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of preventing onset of type I diabetes in mammal predisposed to type I diabetes , comprising implanting insulin-producing cells encapsulated in a biologically-compatible membrane in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

(II) Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" ... wherein said dose is at least one order of magnitude less that that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes" claimed in claim 1 represent a departure from the specification. The passages pointed by the applicant do not provide a clear support for the " ...wherein said dose is at least one order of magnitude less that that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes. The specification and the claims as originally field only support administering a tolerizing dose of insulin-producing cells encapsulated in a biologically-compatible membrane. The passage pointed by Applicant only generally disclosed that curative dose is between one and two orders of magnitude greater than the tolerizing dose.

(7) Response to Argument

(I) Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide **enablement** for a method of preventing onset of Type I diabetes in any mammal , including human comprising implanting insulin-producing cells encapsulated in a biologically compatible membrane.

At page 5 of the Brief, Appellant arguers that one skill in the art would have no difficulty carrying out the steps for making and using the invention, i.e. preventing diabetes. Appellant further submitted that in the first and in the second declaration of Dr. Schart it has been showing that NOD mice receiving the treatment described in the specification were indeed prevented from becoming diabetic. Appellant further submitted that as evidence from provided support in the form of affidavit from the expert and scientific publication, NOD mice is at present the standard model for studying Type I diabetes.

At page 7 of the Brief, Appellant asserts that experimentation to determine screening and testing protocols to demonstrate the efficacy of the claimed invention is not undue.

Contrary to Appellant's assertion, it is noted that the data presented in the declarations of Dr. Scharp under 37 CFR 1.132 clearly indicated that using NOD mice as a model, 40% of the treated animals develop diabetes. In other words, even in NOD animal model in 40 % of the animals the onset of diabetes has not been prevented using the claimed method. In addition, the Examiner acknowledge that NOD mice is at present one of existing model for studying Type I diabetes. However, the issue raised in the Final Office Action was not about preventing diabetes in NOD mice. It remains the Examiner's position that that the data obtained in NOD mice model can not be extrapolated to the claimed method of preventing type I diabetes in any mammals, including human. The specification does not adequately teach how to effectively prevent onset of type I diabetes in any mammal predisposed to type I diabetes , comprising implanting insulin-producing cells encapsulated in a biologically-compatible membrane. Atkinson et al. .,(Nature, 1999, V.5, pages 601-604) teach that in addition to certain NOD strain-specific characteristics that distinguish these mice from humans at risk for type I diabetes important genus-specific features distinguish the murine diabetes as well, such as resistance to ketoacidosis or the absence of the murine homolog of HLA-DR molecules on APC. Investigators have not always considered that. **Unfortunately, in a genetically heterogeneous human population containing individuals at high risk of type I diabetes development, there is little evidence that many of them would have a comparable set of immune deficiencies that prove as malleable** (emphasis added). In NOD mice, type 1 diabetes development is well-choreographed. In contrast, the natural history of type 1

diabetes in human is such that the age of disease onset is extremely broad; symptoms occur at any time from the first years of life to well beyond 50 years of age. It is clear that the genus-unique and strain-specific aspects of diabetes in NOD mice must be fully understand and appreciated if we are to know which therapeutic protocols are reasonable to extrapolate to humans and which are not. Exploitation of the NOD genome for clinical research is yet to be done (see pages 602, 603 and 604 in particular). Knip M (Acta Pediatr. Suppl., 1998, V.452, pages 54-62) teaches that currently the state of the art is that successful prevention of type I diabetes has at least two precondition. First, one must be able to identify individuals at increase risk for progression to type I diabetes and second, must have an intervention modality with less severe adverse effects than those associated with disease itself. Total eradication of clinical type I diabetes cannot be expected in the next century, as it is probable that a combination of different interventions will be needed to achieve an optimal effect (see entire document, page 60 in particular).

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" ... wherein said dose is at least one order of magnitude less that that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes"

claimed in claim 1 represent a departure from the specification.

At page 8 of the Brief, Appellant asserted that the specification at page 4, line 26-27 , at page 9, line 9-11 and at page 19, line 13-19 clearly establishes that the dose for prevention of the diabetes is at least one order of magnitude less than that necessary to achieve normoglycemia in a mammal of the same species.

Contrary to Appellant assertion, it is noted that in the passages pointed by Appellant refers to a method of treating, not preventing , diabetes, comprising **two-step process**:

- implanting a tolerizing doze of insulin-secreting cells , encapsulated in a biologically compatible permselective membrane
- administering to the mammal a curative dose of corresponding unencapsulated insulin-secreting cells.

In other words the specification as originally filed only disclosed two-step process, wherein a tolerizing doze is one to two orders of magnitude less than the curative in the method of treating diabetes.

It is noted that the amended claim 1, now recites a method of preventing type 1 diabetes comprising **only one step, i.e.** implanting a tolerizing doze of insulin-secreting cells , encapsulated in a biologically compatible permselective membrane.

It is also noted that said amendment to claim 1 has been done to overcome the prior rejection of: (i) claims 2-5 and 7-9 under 35 U.S.C. 102(e) as being anticipated by US Patent 6,703,017 or by US Patent 5,425764 and (ii) claims 2-9 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,703,017 or by US Patent 5,425764 each and in view of US Patent 5,529,914 in the non-final Office Action, mailed on 12/16/05. Said rejections have been withdrawn in view of the amended to claim 1. However, as has been stated in the final Office Action mailed on 05/18/05, said rejections will be re-introduced when the **new matter** (wherein said dose is at least one order of magnitude less that that necessary to achieve normoglycemia in a mammal of the same species with type I diabetes) is deleted from claim 1.

(VIII) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(IX) Evidence Appendix

The Evidence Appendix to the brief is correct.

(X) Related Proceeding(s) Appendix

There are no decisions rendered by a court or the Board in any related proceedings.

For the above reasons, it is believed that the rejections should be sustained

Michail Belyavskyi, Ph.D
Art Unit 1644
January 20, 2006

Conferees:

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